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Obesity and risk factors for cardiovascular disease and type 2 diabetes: Investigating the role of physical activity and sedentary behaviour in mid-life in the 1958 British cohort☆

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ABSTRACT

Objective: A key public health priority is to minimise obesity-related health consequences. We aim to establish whether physical activity (PA) or less sedentary behaviour ameliorate associations of obesity with biomarkers for cardiovascular disease (CVD) and type 2 diabetes.
Methods: Data on obesity (33 y), PA (42 y), TV-viewing and health biomarkers (45 y) are from the 1958 British birth cohort ($N = 9377$).
Results: Obesity was associated with an adverse biomarker profile for CVD and type 2 diabetes. For PA, men active ≥1/week had 1.09% (0.28, 1.90) lower diastolic blood pressure (DBP) than less active men; triglycerides were 2.08% (0.52, 3.64) lower per unit higher PA (on 4-point scale). TV-viewing was independently associated with several biomarkers, e.g. per unit higher TV-viewing (on 4-point scale) DBP was raised by 0.50% (0.09, 0.90) and triglycerides by 3.61% (1.58, 5.64). For both TV-viewing and PA, associations with HbA1c were greatest for the obese ($p_{interaction} \leq 0.04$): compared to a reference value of 5.20 HbA1c% in non-obese men viewing 0–1 h/day, HbA1c% differed little for those viewing >3 h/day; among obese men HbA1c% was 5.36 (5.22, 5.51) and 5.65 (5.53, 5.76), for 0–1 and >3 h/day respectively. For PA in non-obese men, the reduction associated with activity ≥1/week was negligible compared to a reference value of 5.20 HbA1c% for those less active; but there was a reduction among obese men, HbA1c % was 5.50 (5.40, 5.59) vs 5.66 (5.55, 5.77) respectively.
Conclusion: Reduced TV-viewing and prevention of infrequent activity have greatest beneficial associations for glucose metabolism among the obese, with benefits for other biomarkers across obese and non-obese groups.

1. Introduction

Health-damaging effects of obesity have been found for mortality, cardiovascular disease, type 2 diabetes and associated risk factors such as blood pressure and lipids [1]. There are also many studies suggesting protective effects of physical activity (PA) and deleterious effects of sedentary lifestyles on all-cause and cardiovascular disease (CVD) mortality[2–4], type 2 diabetes and associated biomarkers, such as blood pressure[5–8]. Some studies demonstrate that obesity, PA and sedentary behaviour have separate contributions to CVD and diabetes-related outcomes [2,4,5,9–13]. In addition to the observational evidence for type 2 diabetes, benefits of PA have been shown in intervention studies that emphasise weight control, PA and dietary modification [14,15]. With increasing trends in obesity, substantial proportions of the global population are now at risk of obesity-related ill-health [16,17]. Strategies to halt the rising trend in obesity are important, but action is needed simultaneously for generations already affected. Thus, a key public health priority is to minimise obesity-related health consequences. In this context, potentially modifiable factors, such as PA and sedentary lifestyles, should be considered.

Observational studies suggest that obese adults may reap greater health benefits from being physically active or less sedentary than the non-obese. In a Finnish study, the impact of leisure-time PA on the risk of death from ischaemic heart disease was stronger in men whose body mass index (BMI) was ≥27 kg/m^2 [18]. For type 2 diabetes, a review of 8 studies found that obese groups who were physically inactive had an increased risk greater than the additional effect of each factor (obesity and inactivity) separately [19], whilst an earlier study had reported stronger protective effects of activity among obese individuals [9]. Yet, not all studies show

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greater benefits of activity amongst obese groups for type 2 diabetes [20] or coronary heart disease [2,5]. Research is scarce on whether benefits of activity vary for obese and non-obese groups across multiple CVD and diabetes biomarkers and whether there are corresponding patterns for sedentary behaviour. The lack of evidence for sedentary behaviour is important given that such behaviours are increasing [21]. As argued elsewhere, interactive effects of activity (or sedentary behaviour) and obesity imply that prevention of either reduces type 2 diabetes risk by abolishing the separate effects of each factor as well as the increased risk due to the interaction between them [19].

We investigated whether obesity-CVD or diabetes biomarker associations can be lessened by PA or lower sedentary behaviour in the 1958 British birth cohort. Our aim was to determine whether obesity, PA and sedentary behaviour were independently associated with biomarkers for CVD and type 2 diabetes and, also, whether PA or sedentary behaviour moderated the obesity − biomarker associations. We investigated the association between obesity in early adulthood (33 y) with CVD and diabetes biomarkers twelve years later (at 45 y) together with PA and sedentary behaviour (indicated by TV-viewing) recorded before or at 45 y. This temporal sequence was used to follow the ordering for potential interventions to reduce the health burden associated with obesity.

2. Methods

2.1. Study sample

The 1958 cohort consists of 17,638 males and females followed from birth during one week, March 1958, in England, Scotland and Wales [22]. Information was collected at several ages throughout child and adulthood. At 45 y, individuals still in contact with the study, and who at 42 y had not required a proxy interview ($n = 11{,}971$) were invited to a home-based clinical assessment by a nurse; the 9377 (78%) who responded were broadly representative of the total surviving cohort [23]. The 45 y survey included blood collection, to which participants gave written informed consent. Ethical approval was given by the South-East Multi-Centre Research Ethics Committee (ref: 01/1/44).

2.1.1. Outcomes

All CVD and diabetes biomarkers were obtained at 45 y from measurements taken by nurses using standardised protocols. After participants were seated for five minutes, blood pressure was measured three times (Omron 705CP, Tokyo, Japan); average systolic and diastolic blood pressure (SBP and DBP) values were used. Non-fasted venous blood samples were obtained and posted to a central laboratory. Glycosylated haemoglobin (HbA1c) levels were measured using ion exchange high performance liquid chromatography. Total-, HDL-cholesterol and triglyceride levels were analysed by an autoanalyzer (Olympus AU640, Japan) using enzymatic methods. LDL-cholesterol was calculated using the Friedewald formula [24], except when triglyceride levels were >4.5 mmol/l. Nurses recorded currently prescribed medications (observed from packaging) from which we identified type 2 diabetes, anti-hypertensive and lipid-lowering medications.

2.1.2. Obesity, PA and sedentary behaviour

Height and weight were measured at 33 y using standardised protocols and BMI calculated as weight/height^2 (kg/m^2). Obesity was defined as BMI $\geq$ 30 kg/m^2. Also, we identified i) the top BMI quintile at 33 y (men $\geq$ 28 kg/m^2; women $\geq$ 27 kg/m^2); ii) 42 y obesity, from BMI based on self-reported weights and heights; and iii) 45 y obesity, from waist circumference (measured midway between the lower ribs and iliac crest) using cut-offs: $\geq$102 cm for men; $\geq$88 cm for women.

Leisure-time PA at 42 y was assessed using a question about frequency of regular activity (to aid recall, several activities were provided as examples) categorised into four groups: $\leq$2–3 times/month, once/week, 2–3 times/week and 4–7 times/week. For leisure-time sedentary behaviour we used self-reports at 45 y of average daily TV-viewing in the previous year, in four groups (0–1 to $\geq$3 h/day).

2.1.3. Covariates

Several covariates were identified from the literature. Birthweight was recorded prospectively, measured in pounds and ounces, and converted into kilograms. Smoking, reported at 33 y, was categorised as never, ex-smoker, or current smoker. Socioeconomic position (SEP), based on the Registrar General's Social Classification of their occupation at 33 y, was categorised into four groups: I (professional) or II; IIINM; IIIM; and IV or V (unskilled). Highest qualification by 33 y was categorised into five groups: none, some, O-levels, A-levels or degree. Longstanding illness, disability or infirmity limiting daily activities were identified at 33 y. Diet at 33 y included consumption frequency of fruit (five categories: <1 day/wk to >1/day), chips (five categories: 1+/day to never) and alcohol (five categories: most days to never). For women, hormone replacement therapy (HRT), oral contraceptive (OC) and menopausal status were ascertained at 45 y. Hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg [25] or on medication for high blood pressure) was a covariate for some biomarkers.

2.2. Statistical analyses

To facilitate comparison, all biomarkers were log-transformed and multiplied by 100; in analyses, regression coefficients are interpreted as symmetric percentage differences in means [26]. To avoid possible bias in associations that can occur by excluding participants using medications or by ignoring medication use, we followed the recommendation to correct biomarker levels [27]. For individuals on medication for high blood pressure ($n = 424$) we corrected values by +10 mmHg for DBP and SBP respectively [27]; for oral medication for type 2 diabetes ($n = 122$) +1% in absolute terms for HbA1c [28] and for lipid-lowering drugs ($n = 126$) +25% for total-cholesterol, +54% for LDL-cholesterol, +18% for triglycerides, −5% for HDL-cholesterol [29]. Individuals with type I diabetes ($n = 56$) were excluded from analysis of HbA1c.

Preliminary work showed that several 33 y obesity, 42 y PA and 45 y TV-viewing associations with biomarkers varied by sex ($p_{\text{interaction}} < 0.02$), hence, we assessed associations separately for men and women. In preliminary analysis we also found no trend in blood pressure or HbA1c across categories of increasing activity frequency, except between the least active ($\leq$2–3 times/month) and others. Thus, for these biomarkers we treated activity as a dichotomous variable, but as a continuous variable for other biomarkers. Associations for TV-viewing and biomarkers showed trends across the four categories, so TV-viewing was treated as continuous in all analyses. Linear regression models were undertaken as follows: Model 1, unadjusted; Model 2, adjusted for covariates; and Model 3, adjusted for covariates plus the two other main exposures (i.e. BMI, PA or TV-viewing as appropriate). To account for co-morbidity, adjustments were made for hypertension and total- and HDL-cholesterol. For all biomarkers, we tested interactions (i.e. effect modification) between obesity and (i) PA or (ii) TV-viewing. To establish whether any interactions ($p < 0.05$) were due to differences in adiposity concurrent with biomarker measurement, we further adjusted for 45 y BMI and waist

circumference. Because we used linear regression, interactions reported refer to departure from additivity.

We examined the impact of fieldwork factors, including examination month, time of day, recent food consumption, temperature, batch and sample delivery time to the laboratory. All showed negligible influences on associations of interest (data not shown). We conducted sensitivity analyses using three alternative definitions of adult obesity (top 33 y BMI quintile, 42 y obesity and 45 y central obesity indicated by waist circumference). Unless stated, results for 33 y obesity were confirmed with at least one of these alternative measures. Of 9377 participants in the 45 y clinical survey, 4644 males and 4690 females had data on ≥1 biomarker ($N = 3562–4632$ in males; 3817–4665 in females). To minimise data loss and potential bias due to missing information, missing covariates were imputed using multiple imputation chained equations and regression analyses were run across 10 datasets. Imputed models included predictors of non-response (i.e. cognitive ability and behaviour at 7 y, SEP at birth and in adulthood [23]). We repeated analyses using the maximum, non-imputed, available sample; associations were broadly similar to those using imputation. The latter are reported here.

3. Results

At 33 y, approximately 10% of the population were obese, about a third were active ≤2–3 times/month at 42 y and ~23% watched TV for >3 h/day at 45 y (Table 1).

3.1. Obesity

In both sexes, 33 y obesity was associated with lower HDL-cholesterol at 45 y and higher SBP, DBP, HbA1c, triglycerides and, additionally in women, with higher LDL-cholesterol. Associations for obesity attenuated after adjustment, but were largely independent of PA, TV-viewing and other covariates. In men, the estimated associations ranged from 4.30% (95% confidence interval (CI) 3.19, 5.41) to 20.2% (13.7, 26.7) and in women, from 4.93% (3.65, 6.20) to 24.7% (18.9, 30.4) higher SBP and triglycerides respectively (Fig. 1a). Adjusted (percentage) differences are shown in Table 2 together with mean differences (in units), e.g. in obese men SBP was elevated by an average of 5.7 mmHg and HbA1c% by 0.45.

3.2. Physical activity

PA at 42 y was associated with elevated HDL-cholesterol in both sexes and lower total- and LDL-cholesterol and triglycerides in men per unit higher activity level on the 4-point scale (Fig. 1b). Associations attenuated after adjustment for covariates, then weakened further after adjustment for 33 y BMI and 45 y TV-viewing: an association remained in men of 2.08% (0.52, 3.64) lower triglycerides per unit higher activity level (Table 2). These results suggest that PA was associated with blood lipids via BMI and/or TV-viewing. For blood pressure and HbA1c, those active at least once a week had lower levels than the infrequently (≤2–3 times/month) active. Associations were mostly abolished after adjustment. However, in men, DBP was lower by 1.09% (0.28, 1.90) after adjustment for covariates including BMI and TV-viewing (from 1.47% (0.65, 2.29) in model 1) (Fig. 1b). Also in men, the association between PA and HbA1c varied for obese and non-obese groups, with a stronger association in the obese ($p_{interaction} = 0.04$) (Fig. 2a). To illustrate, from a reference value of 5.20 HbA1c% in non-obese infrequently active men, there was no reduction for active men (with HbA1c% 5.22 (5.18, 5.26)); whereas, in the obese there was a reduction associated with activity, from 5.66 (5.55, 5.77) HbA1c% for infrequently active to 5.50 (5.40, 5.59) for active men. The interaction between PA and 33 y obesity on HbA1c persisted after further adjustment for 45 y adiposity. No interactions were found of PA and obesity on blood lipids and an interaction for SBP seen only in women ($p_{interaction} = 0.03$) was not confirmed in sensitivity analyses using alternative definitions of adult obesity.

3.3. TV-viewing

Higher levels of 45 y TV-viewing were associated with lower HDL-cholesterol and increased DBP, SBP, HbA1c and triglycerides in both sexes and, in women, also with total- and LDL-cholesterol

Table 1
CVD biomarkers, PA and TV-viewing for obese and non-obese groups at age 33 y in the 1958 cohort.[a]

CVD biomarkers 45 y	Men			Women		
	Total ($N = 3977$)	Obese ($N = 390$)	Non-obese ($N = 3587$)	Total ($N = 4178$)	Obese ($N = 443$)	Non-obese ($N = 3735$)
	Mean (SD)			Mean (SD)		
DBP (mmHg)	82.2 (10.3)	85.2 (9.58)	81.9 (10.4)	75.7 (10.3)	80.4 (10.8)	75.2 (10.1)
SBP (mmHg)	133.0 (14.8)	137.6 (13.8)	132.4 (14.8)	120.5 (15.6)	127.0 (17.9)	119.7 (15.1)
HbA1c (%)[b,c]	5.25 (5.24, 5.3)	5.59 (5.48, 5.70)	5.22 (5.21, 5.24)	5.14 (5.13, 5.16)	5.51 (5.41, 5.60)	5.10 (5.09, 5.12)
Total-cholesterol (mmol/l)	6.07 (1.14)	6.11 (1.26)	6.07 (1.13)	5.70 (0.99)	5.75 (1.07)	5.69 (0.98)
LDL-cholesterol (mmol/l)	3.58 (0.92)	3.59 (0.98)	3.58 (0.92)	3.29 (0.86)	3.39 (0.86)	3.28 (0.86)
HDL-cholesterol (mmol/l)	1.44 (1.69)	1.30 (0.31)	1.45 (0.33)	1.69 (0.41)	1.43 (0.32)	1.72 (0.40)
Triglycerides (mmol/l)[b]	2.08 (2.04, 2.12)	2.55 (2.38, 2.73)	2.04 (2.00, 2.08)	1.37 (1.34, 1.39)	1.85 (1.75, 1.96)	1.32 (1.30, 1.34)
PA 42 y	***N* (%)**			***N* (%)**		
<=2–3 times/month	1269 (33)	158 (41.7)	1111 (32.0)	1385 (34.0)	190 (43.4)	1195 (32.8)
1 time/week	799 (20.8)	74 (19.5)	725 (20.9)	710 (17.4)	80 (18.3)	630 (17.3)
2–3 times/week	857 (22.3)	70 (18.5)	787 (22.7)	868 (21.3)	74 (16.9)	794 (21.8)
4–7 times/week	926 (24.1)	77 (20.3)	849 (24.5)	1117 (27.4)	94 (21.5)	1023 (28.1)
TV-viewing 45 y						
<1 h/day	479 (12.4)	31 (8.2)	448 (12.9)	611 (15.0)	43 (10.1)	568 (15.5)
1–2 h/day	1386 (35.9)	117 (30.8)	1269 (36.4)	1372 (33.6)	116 (27.1)	1256 (34.4)
2–3 h/day	1110 (28.7)	111 (29.2)	999 (28.7)	1210 (29.6)	136 (31.8)	1074 (29.4)
3+ h/day	891 (23.1)	121 (31.8)	770 (22.1)	891 (21.8)	133 (31.1)	758 (20.7)

N varies due to missing data.
[a] Participants with data for ≥1 biomarker and 33 y BMI (667 males and 512 females missing 33 y BMI).
[b] Geometric mean (95% CI).
[c] Excludes those with Type I diabetes.

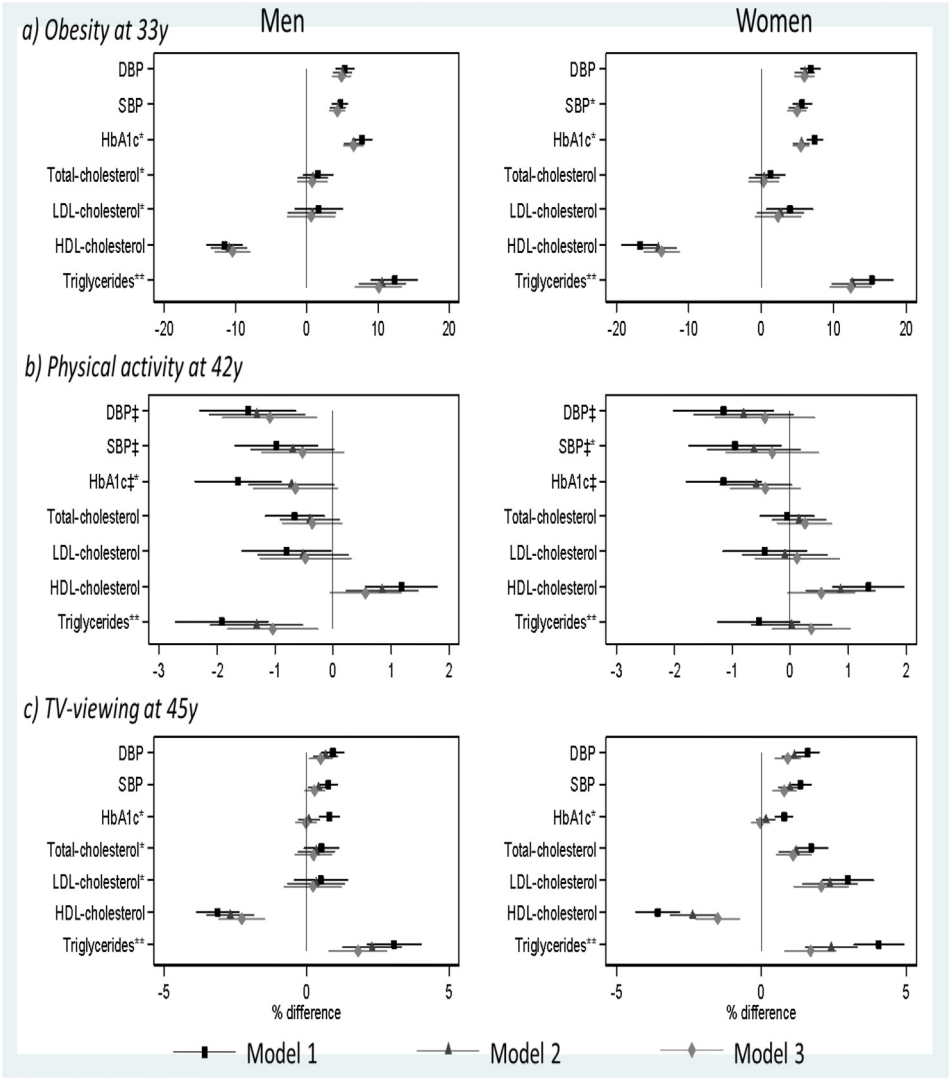

Fig. 1. Associations of obesity (33y), physical activity (42y) and TV-viewing (45y) with CVD/diabetes biomarkers at 45y. Estimated % differences (95% CI) for each biomarker associated with (a) obesity; (b) per unit increase in PA across 4-point scale (≤2–3 times/month to 4–7 times/wk), except for ‡ indicating difference between 1+/wk vs ≤2–3/mo; and (c) per unit higher TV-viewing across 4-point scale (0–1 to ≥3 h/day). *Effect modification present (see text). **Represents a 0.5% change in triglyceride level (multiply by 2 for % change). Model 1 = unadjusted. Model 2 = adjusted for covariates (birth-weight, adult smoking, SEP, qualifications, limiting illness, fruit, chips and alcohol consumption, total- and HDL-cholesterol (for outcomes except lipids) and hypertension (except for SBP and DBP); additionally for women: menopausal status, HRT and OC use). Model 3 = adjusted for model 2 covariates plus other main exposures (a) obesity: PA + TV-viewing; (b) PA: BMI + TV-viewing; (c) TV-viewing: BMI + PA.

(Fig. 1c). Associations attenuated, and in some instances were abolished, after adjustment for covariates including BMI and PA. Notwithstanding, independent associations were found for several biomarkers: per category higher TV-viewing, estimated associations in men ranged from 0.50% (0.09, 0.90) to 3.61% (1.58, 5.64) elevated DBP and triglycerides respectively, and from 0.80% (0.39, 1.21) to 3.39% (1.64, 5.15) higher SBP and triglycerides respectively in women (Table 2). For HbA1c, Fig. 2 shows a trend of higher levels with greater TV-viewing among those who were obese, but not among the non-obese ($p_{\text{interaction}} < 0.01$). TV-viewing > 3 h/day was associated with an 8–9% higher HbA1c in obese men and women relative to non-obese viewing 0–1 h/day. For example, from a reference value of 5.20 HbA1c% in non-obese men viewing 0–1 h/day, no detrimental association was found for those viewing >3 h/day (their value was 5.17 (5.11, 5.23)); whereas in obese men, HbA1c% increased from 0–1 h/day to >3 h/day (5.36 (5.22, 5.51) to 5.65 (5.53, 5.76)). These estimates from adjusted models illustrate the greater detrimental association between HbA1c and higher TV-viewing among the obese. The interaction persisted after further adjustment for 45 y adiposity (data not presented). There was also variation between obese and non-obese groups in associations of TV-viewing with total- and LDL-cholesterol, but in men only ($p_{\text{interaction}} = 0.03$ and 0.04 respectively): a weak positive trend was seen in the non-obese, with a trend in the opposite direction for obese men (Fig. 2b).

4. Discussion

Our study highlights the importance of obesity at 33 years for adult CVD and diabetes biomarkers twelve years later at 45 y. Associations for obesity were largely independent of other factors such as birth-weight, adult smoking, PA and TV-viewing; they were also strong, with biomarker levels elevated by 4.3% (mean difference 5.7 mmHg) for SBP in men to 25% (0.25 mmol/l) for triglycerides in women. Given that effective treatment for obesity at the population level is not currently available, our study was

Table 2
Associations of obesity (33 y), PA (42 y) and TV-viewing (45 y) with CVD/diabetes biomarkers at 45 y. Estimated (i) % difference and (ii) mean difference (in biomarker units) from adjusted models.

CVD biomarkers at 45 y	Men		Women	
	(i) % Difference (95% CI)	(ii) Mean difference (95% CI)	(i) % Difference (95% CI)	(ii) Mean difference (95% CI)
33 y Obesity				
DBP (mmHg)	4.89 (3.60, 6.19)	4.07 (2.99, 5.15)	5.91 (4.57, 7.25)	4.67 (3.63, 5.71)
SBP (mmHg)	4.30 (3.19, 5.41)	5.75 (4.22, 7.27)	4.93 (3.65, 6.20)	6.34 (4.76, 7.93)
HbA1c (%)[a]	6.57 (5.23, 7.91)	0.45 (0.30, 0.61)	5.50 (4.40, 6.59)	0.36 (0.24, 0.49)
Total-cholesterol (mmol/l)	0.78 (−1.32, 2.88)	0.07 (−0.06, 0.20)	0.31 (−1.73, 2.36)	0.03 (−0.09, 0.14)
LDL-cholesterol (mmol/l)	0.63 (−2.74, 3.99)	0.04 (−0.08, 0.16)	2.31 (−0.88, 5.50)	0.07 (−0.03, 0.18)
HDL-cholesterol (mmol/l)	−10.4 (−12.9, −7.94)	−0.15 (−0.18, −0.11)	−13.7 (−16.2, −11.2)	−0.22 (−0.26, −0.18)
Triglycerides (mmol/l)[b]	20.2 (13.7, 26.8)	0.20 (0.14, 0.27)	24.7 (18.9, 30.4)	0.25 (0.19, 0.30)
42 y PA				
DBP (mmHg)*	−1.09 (−1.90, −0.28)	−0.92 (−1.60, −0.25)	−0.44 (−1.30, 0.42)	−0.36 (−1.02, 0.31)
SBP (mmHg)*	−0.52 (−1.23, 0.18)	−0.71 (−1.68, 0.26)	−0.31 (−1.10, 0.49)	−0.33 (−1.32, 0.66)
HbA1c (%)*[a]	−0.65 (−1.37, 0.08)	−0.04 (−0.09, 0.01)	−0.43 (−1.03, 0.18)	−0.02 (−0.06, 0.02)
Total-cholesterol (mmol/l)	−0.36 (−0.87, 0.16)	−0.02 (−0.05, 0.01)	0.25 (−0.22, 0.72)	0.01 (−0.01, 0.04)
LDL-cholesterol (mmol/l)	−0.47 (−1.26, 0.31)	−0.02 (−0.04, 0.01)	0.12 (−0.61, 0.85)	0.00 (−0.03, 0.02)
HDL-cholesterol (mmol/l)	0.56 (−0.05, 1.17)	0.01 (−0.001, 0.02)	0.53 (−0.04, 1.11)	0.01 (−0.002, 0.02)
Triglycerides (mmol/l)[b]	−2.08 (−3.64, −0.52)	−0.02 (−0.04, −0.01)	0.72 (−0.63, 2.06)	0.01 (−0.01, 0.02)
45 y TV-viewing				
DBP (mmHg)	0.50 (0.09, 0.90)	0.41 (0.07, 0.75)	0.92 (0.48, 1.36)	0.69 (0.35, 1.03)
SBP (mmHg)	0.29 (−0.06, 0.63)	0.38 (−0.09, 0.85)	0.80 (0.39, 1.21)	1.00 (0.49, 1.51)
HbA1c (%)[a]	−0.02 (−0.39, 0.35)	0.00 (−0.03, 0.02)	−0.03 (−0.34, 0.28)	0.001 (−0.02, 0.02)
Total-cholesterol (mmol/l)	0.23 (−0.41, 0.88)	0.02 (−0.02, 0.06)	1.12 (0.52, 1.72)	0.06 (0.03, 0.10)
LDL-cholesterol (mmol/l)	0.22 (−0.78, 1.22)	0.01 (−0.03, 0.04)	2.07 (1.14, 3.00)	0.07 (0.04, 0.10)
HDL-cholesterol (mmol/l)	−2.28 (−3.08, −1.47)	−0.03 (−0.04, −0.02)	−1.50 (−2.27, −0.74)	−0.03 (−0.04, −0.01)
Triglycerides (mmol/l)[b]	3.61 (1.58, 5.64)	0.04 (0.02, 0.06)	3.39 (1.64, 5.15)	0.03 (0.02, 0.05)

Associations are estimated differences (95% CI) for each biomarker and (a) obesity; (b) a unit increase in PA across four groups (≤2–3 times/month to 4–7 times/wk), except for * indicating difference between 1+/wk vs <=2–3/mo; and (c) a unit increase in TV-viewing across four groups (0–1 to ≥3 h/day). Adjustments are as indicated for Model 3 in Fig. 1: Model 2 covariates plus the two other main exposures (i.e. for (a) obesity: PA + TV-viewing; (b) PA: BMI + TV-viewing; (c) TV-viewing: BMI + PA).

[a] Robust SEs used for mean difference regression and excludes those with Type 1 diabetes.

[b] Geometric mean (units apply only to estimated mean difference).

motivated to identify factors that ameliorate obesity-related diabetes and CVD risks. In this regard, a main finding was the independent association of TV-viewing with several biomarkers at 45 y. Associations were graded across duration (h/day) categories, such that DBP was elevated by 1.2 mmHg and triglycerides by 0.12 mmol/l in those viewing >3 vs 0–1 h/day. These findings suggest that reductions in h/day TV-viewing would benefit CVD biomarker levels in obese and non-obese groups alike. For glucose metabolism, a main finding was the stronger associations of TV-viewing with HbA1c among obese than non-obese men and women, and consistent with this finding was the greater protective association of PA on HbA1c in obese men.

4.1. Methodological considerations

Strengths of the cohort for this investigation include large sample size, general population coverage and combination of data on obesity, PA, TV-viewing and multiple biomarker measures. We used a temporal sequence for age of obesity, PA (or TV-viewing) and biomarker measures, to mirror the timing of an activity or sedentary behaviour intervention targeted at obese and non-obese groups. The life-stage provides a further advantage, as chronic disease is relatively uncommon for the ages studied, hence reverse causation, e.g., from diabetes or CVD risk to BMI or PA, is less of a concern than at older ages when chronic disease is more common. Information available allowed us to control for several factors that could confound associations (e.g. we controlled for prior illness and co-morbidity that might affect activity levels) or act as mediators (e.g. diet could mediate associations for TV-viewing). Despite its limitations, we relied on BMI to indicate obesity. Obesity at 33 y may be too distant from biomarker measures but associations, including the interaction with TV-viewing on HbA1c, were confirmed in sensitivity analyses using obesity measures at later ages (i.e. based on 42 y BMI and 45 y waist circumference) in all but one instance. We have focussed on PA and sedentary behaviour as potential modifying influences on obesity – biomarker associations; other factors such as diet may warrant attention. Our adult PA and sedentary behaviour measures are self-reported, simple questionnaire-based measures, widely used in large populations because of practicality and low cost. Such measures have limitations, e.g. demands of recall, and are likely to be affected by measurement error [30]. More consistent associations were observed for TV-viewing than PA, possibly due to its proximity to biomarker assessment at 45 y, whereas PA was reported at 42 y; furthermore, TV-viewing was reported in h/day, whereas PA was frequency/week with no information on type or duration. Although commonly used, it is unclear whether TV-viewing is an adequate indicator of sedentary lifestyle. It omits other leisure-time and occupational sedentary behaviours, although >75% of our adults used computers in leisure <1 h/day and sitting at work shows few weak associations with CVD biomarkers in this population [31]. The socio-demographic and lifestyle characteristics of individuals with greater TV-viewing represent a more adverse diabetes and CVD risk profile [31], raising the possibility of residual confounding. For example, our study does not take account of familial history of cardiovascular risk. Glucose metabolism was indicated by HbA1c because it was impractical to obtain fasting samples in this nationwide, working-age population. While total- and HDL-cholesterol are little affected, triglycerides are lower after fasting and vary by duration of fasting and time of day. Fasting and non-fasting triglycerides are positively correlated [32], and a meta-analysis found no variation in results for triglycerides by fasting

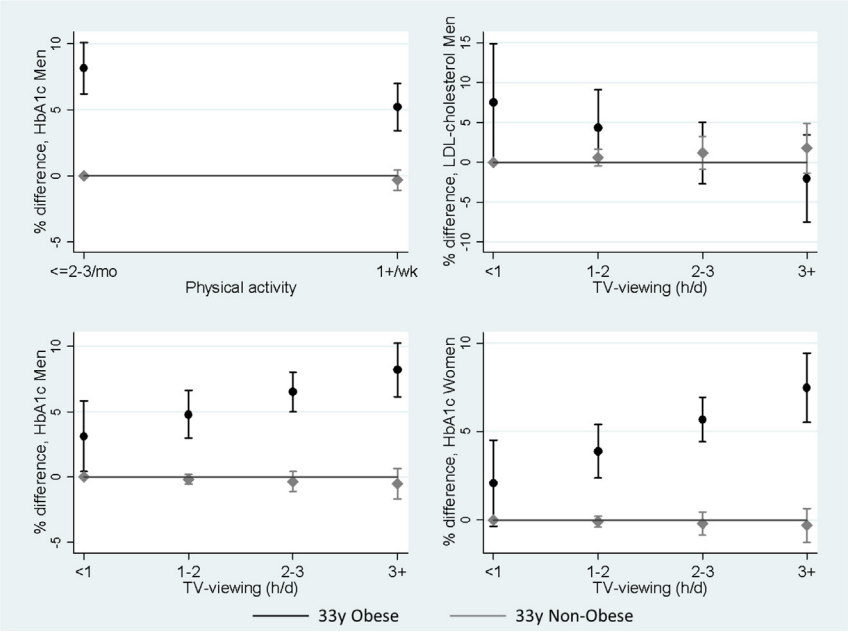

Fig. 2. Associations of physical activity (42y) or TV-viewing (45y) with obesity (33y) for HbA1c or LDL-cholesterol at 45y. Estimated % difference (95% CI) in HbA1c or LDL-cholesterol for obese and non-obese, by level of PA or TV-viewing (fully adjusted, i.e. Model 3).

status [33], suggesting that such measures are useful in large epidemiological studies. Finally, there has been sample attrition over the years of follow-up in our study. To avoid further loss of data, we used imputation for missing information on covariates.

4.2. Interpretation and comparison with other studies

Our finding that 33 y obesity was associated with several diabetes and CVD biomarkers at 45 y, adds to an extensive literature on obesity-related health hazards [1]. Similarly, the observation that associations were largely independent of PA and sedentary behaviour agrees with previous studies [5]. Associations for 33 y obesity may not be as strong as for concurrent obesity: e.g., mean SBP was raised by 5.2 (4.5, 5.9) mmHg for 33 y obesity compared to 6.9 (6.2, 7.5) mmHg for 45 y obesity [34]. Hence, our estimates of obesity-related disease risk will be conservative.

In considering whether PA or reduced sedentary behaviour could ameliorate the adverse biomarker profile related to obesity, our study adds to existing evidence in two important respects. First, the stronger trend of HbA1c with TV-viewing among obese than non-obese groups is a novel finding, as few studies investigate such variations for sedentary behaviour separately from lack of PA. The role of prolonged sedentary behaviour for elevated risk of diabetes was highlighted by a systematic review and meta-analysis [8], whilst, deleterious effects on glucose levels of uninterrupted compared to interrupted sitting were found in an experimental study of overweight middle-aged adults [35]. Our findings suggest that adverse effects of sedentary behaviour, indicated by longer TV-viewing, are particularly pronounced for obese men and women. Because the interaction of TV-viewing with obesity on HbA1c remained after adjustment for current adiposity, suggests that greater adiposity gain, 33–45 y, among those with higher TV-viewing levels is an unlikely explanation for our finding. Correspondingly, we found a greater benefit of PA at least weekly on HbA1c among obese than non-obese men. This finding agrees with a recent study [6] and a review on risk of type 2 diabetes [19]. The review reported additive effects of PA and obesity (i.e. the joint effect was more than the sum of individual effects) and argued that inactivity mainly interacts with obesity to cause diabetes, instead of through an independent pathway [19]. From a public health perspective, such associations are important because, as seen in our population, the obese group at 33 y was less likely than others to be active subsequently at 42 y and more likely to watch TV for >3 h/day at 45 y. These differences had occurred at a time of increasing trends in sedentary lifestyles [21]. Interestingly, diabetes intervention studies have shown benefits of lifestyle modification in high BMI groups [14,15], for whom our study suggests the greatest improvements in glucose metabolism can be gained. Apart from HbA1c, effect modification of obesity risks by TV-viewing or PA was either absent or not confirmed in sensitivity analysis (e.g. for PA and obesity on SBP among women). Opposing trends of TV-viewing with total- and LDL-cholesterol seen for obese and non-obese men, suggest that benefits from reduced sedentary behaviour are less likely after obesity onset, although other studies are needed to corroborate this finding.

Second, our study adds to the evidence-base on the separate contribution of TV-viewing and PA to CVD biomarker levels. Independent associations were observed, particularly for TV-viewing among women, suggesting that there may be benefits of reduced TV-viewing for obese and non-obese groups alike. Given that biomarker levels worsen with each increment of TV-viewing implies that, if causal, any reduction in viewing h/day has the potential to improve biomarker profiles. Similarly, a graded association was found for PA and triglycerides, with protective associations for each increment of activity frequency. For blood pressure and HbA1c, the association for those active at least weekly vs less frequently, rather than a graded association, suggests that there may be a threshold for protective effects associated with PA for these biomarkers.

To conclude, our study suggests that reductions in TV-viewing and increased activity have the potential to minimise the effect of obesity on glucose metabolism in middle-aged adults. Whether such findings could motivate individuals to be less sedentary and more active remains to be explored. Higher rates of sedentary behaviour among obese groups are a concern given its association with several biomarkers. Our study raises the prospect that there

will be stronger detrimental effects on future mortality of sedentary behaviour or inactivity in obese groups.

Author contributions

CP had the initial conception of the study and has drafted the paper. SPP undertook analyses. All authors contributed to the study design and interpretation of results, and all have revised the paper and approved the final version to be published. CP and SPP are guarantors for the study.

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Conflict of interest

The authors declare that they have no conflict of interest.

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